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10/765,264	01/27/2004	Darryl J.C. Pappin	BP0207-US 2	9574

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EXAMINER

GAKH, YELENA G

ART UNIT	PAPER NUMBER
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1797

MAIL DATE	DELIVERY MODE
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05/20/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/765,264	Applicant(s) PAPPIN ET AL.	
	Examiner Yelena G. Gakh, Ph.D.	Art Unit 1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 March 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4-8,15,27,47,50 and 51 is/are rejected.
- 7) ☒ Claim(s) 1 and 27 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>06/09/08, 04/03/09</u> . | 6) <input type="checkbox"/> Other: _____ |

Continuation of Disposition of Claims: Claims pending in the application are 1,4-13,15,16,18,19,26,27,29-33,35,38-42,44-47,50,51,93,94,96,97,99,101,105,106,110,111 and 113.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 9-13,16,18,19,26,29-33,35,38-42,44-46,93,94,96,97,99,101,105,106,110,111 and 113.

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DETAILED ACTION

1. Amendment filed on 03/06/09 is acknowledged. Claims 2-3, 14, 17, 20-25, 28, 34, 36-37, 43, 48-49, 52-92, 95, 98, 100, 102-104, 107-109, 112 and 114 are cancelled. Claims 1, 4-13, 15-16, 18-19, 26-27, 29-33, 35, 38-42, 44-47, 50-51, 93-94, 96-97, 99, 101, 105-106, 110-111 and 113 are pending in the application. Claims 9-13, 16, 18-19, 26, 29-33, 35, 38-42, 44-46, 93-94, 96-97, 99, 101, 105-106, 110-111 and 113 are withdrawn from consideration. Claims 1, 4-8, 15, 27, 47 and 50-51 are considered on merits.

Examiner's note: some dependent claims, e.g. claims 38-42, 44-46, depend on cancelled claims 36 and 37.

Since currently amended claim 42 depends on the cancelled claim 37, it is not considered on merits.

Response to Amendment

2. The amendment filed 03/06/09 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "at least each of two peptide samples with labeling reagent [to] produce two or more differentially labeled samples, wherein each labeling reagent comprised of one or more heavy atom isotopes and a reporter moiety comprising a substituted or non substituted morpholine, piperidine or piperazine compound or a salt thereof and wherein the gross mass of each reporter is different for each reagent of the set".

Applicant is required to cancel the new matter in the reply to this Office Action.

3. In response to the amendment the examiner modifies all rejections and adds objection to the claims.

Claim Objections

4. Claim 1 is objected to because of the following informalities: in the amended claim the expression in step a), "reacting at least each of two peptide samples with a labeling reagent produce two or more differentially labeled samples", does not sound grammatically correct. It looks like "to" should be inserted before "produce". Appropriate correction is required.

5. Claim 27 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the

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claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The reporter moiety comprising substituted morpholine, piperidine or piperazine compound, do not substantially sub-fragment, and therefore the recitation of claim 27 does not further limit the structure of the reporter molecule recited in the parent claim.

Specification

6. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

- (a) TITLE OF THE INVENTION.
- (b) CROSS-REFERENCE TO RELATED APPLICATIONS.
- (c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
- (d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
- (e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
- (f) BACKGROUND OF THE INVENTION.
 - (1) Field of the Invention.
 - (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
- (g) BRIEF SUMMARY OF THE INVENTION.
- (h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
- (i) DETAILED DESCRIPTION OF THE INVENTION.
- (j) CLAIM OR CLAIMS (commencing on a separate sheet).
- (k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
- (l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to as not containing a written description of the invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same".

The specification is not arranged in the manner provided by the guidance, which ensures a clear and concise description of the invention, and in general is written in unclear and vague language in regards to the subject matter considered by the Applicants as inventive and non-obvious over the prior art. The specification does not contain a Summary of the Invention which allows understanding, as to what specifically the Applicants consider the essence of their invention. In combination with the vague and indefinite language of the claims, which recite "a method, comprising" reacting two or more samples with reactive analytes and mixing the products of the reaction (e.g. Claim 1), the specification does not meet the requirements of the first paragraph of 35 U.S.C. 112. The description of the "Field of the Invention" as "analyte determination by mass analysis" is so general and broad, that it does not reflect to any extent the inventive subject matter. The only specific disclosure provided in the specification in regards to the claimed subject matter is related to specific examples, which therefore will be considered as the only enabling disclosure of the instant application. In other words, the only enabling disclosure is pertained to specific examples, which disclose proteomic analysis based on mass spectrometry of specifically labeled proteins with the labels provided in the examples and the proteins being extracted, digested and separated. Moreover, not all specific labels disclosed in the specification enable performing the method, since e.g. there is no experimental evidence for thiocarbonyl linker to be capable of providing the function required by the instant method, taking into account the reactivity of thiocarbonyl compounds (see page 50, lines 12-17).

The examiner will accept any changes in the specification, which will not introduce new matter to the disclosure, but which will help to clarify the essence of the invention.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 4-8, 15, 27, 47 and 50-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The examiner respectfully reminds the Applicants that according to MPEP §2163:

"2163.02. Standard for Determining Compliance with Written Description Requirement:

The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)). Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Claim 1 recites:

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"reacting at least each of two peptide samples with labeling reagent [to] produce two or more differentially labeled samples, wherein each labeling reagent comprised of one or more heavy atom isotopes and a reporter moiety comprising a substituted or non-substituted morpholine, piperidine or piperazine compound or a salt thereof and wherein the gross mass of each reporter is different for each reagent of the set". The examiner failed to find this language in the specification. The specification discloses the following:

"In some embodiments, the kit can comprise one or more isobarically labeled reagents of the formula [formulas are provided on pages 42-47, with all formulas comprising the carbonyl group] ... wherein ... isotopes of carbon-13, oxygen-18 and nitrogen-15 are used to balance the gross mass between the reporter and the carbonyl linker of the different labeling reagents". The disclosure is different from the subject matter recited in the claims. Therefore, the Applicants did not reasonably convey to those skilled in the art that they "had possession at that time of the later claimed subject matter".

10. Claims 1, 4-8, 15, 27, 47 and 50-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method comprising labeling samples with isobaric labels, with the isobaric labels being ones given by the specific structural formulas represented on pages 42-47 and meeting the balancing condition for the gross mass, as provided above, does not reasonably provide enablement for any other method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. It would have been an undue experimentation for a person of ordinary skill in the art to search for proper labeling reagents in order to perform proteomic analysis by mass spectrometry as recited in the instant claims, since the disclosure is specifically directed toward isobaric labeling of the peptide analytes.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claim 1 recites, "reacting at least each of two peptide samples". It is not apparent, as to what the expression "at least" refers to. Is this supposed to be "reacting each of at least two peptides"?

Further, the claim recites that the sample is reacted with a labeling reagent - is this the same labeling reagent, or different labeling reagents? This difference is essential for performing the method, and unclarity as to whether this is the same labeling reagent for both samples, or two different labeling reagents, renders the claim and all dependent claims unclear and indefinite.

Further, the claim recites "each labeling reagents is comprised of one or more heavy atom isotopes and a reporter moiety". What "heavy atom isotopes" are meant here? The periodic table comprises 110 elements, all of which comprise different isotopes, with at least hundred being "heavy atoms". The terminology "heavy atom isotopes" makes it totally unclear, as to which isotopes are meant in the claim. It is also unclear, how the reporter moiety is structurally related to the heavy atom isotopes.

Further, the claim recites "wherein the gross mass of each reporter is different for each reagent of the set". No "set" has been previously recited in the amended claim, and therefore it is not clear, which "set" is meant. This limitation does not have an antecedent basis. Also, is "reporter" the same as "reporter moiety"?

Step b) recites "mixing the two or more differentially labeled samples". This step is unclear - if the samples are separate, then why should they be mixed in order to be analyzed? The step is unclear.

The language of the claim renders it and all dependent claims unclear and indefinite.

Claim Rejections - 35 USC § 103

13. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

14. **Claims 1, 4-8, 15, 27, 47 and 50-51** are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al. (Nature Biotechnology, 2002) (Zhou) in view of Van Ness et al. (EP 0990047 B1) (Van Ness).

Regarding claims 1 and 4-6 and 27 Zhou teaches "quantitative proteome analysis by solid-phase isotope tagging and mass spectrometry" (Title), comprising tandem LC-MS/MS

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spectrometry of at least two peptide samples tagged with isotopically enriched labels comprising different heavy atom isotopes and reporter moieties (see page 512 and Figure 1), which means that

the at least two peptide samples are reacted with a labeling reagent comprising "a heavy atom isotope" and a reporter moiety,

tandem MS/MS analysis is performed, i.e. steps c) and d).

Internal standard is added to the mixture (see page 514, right column, first paragraph).

Zhou discloses reporter moieties being substituted aromatics, rather than substituted or non-substituted morpholine, piperidine or piperazine compound.

Van Ness discloses a method of detecting nucleic acids with mass spectrometry using labeling reagents comprising substituted aromatics, as well as substituted or non-substituted morpholine, piperidine or piperazine compound. The important feature of reporter moieties for both peptides and nucleic acids MS/MS detection is the presence of amino group, which makes reporter moieties disclosed by Van Ness suitable for Zhou's method.

Thus, it would have been obvious for a person of ordinary skill in the art to substitute aromatic reporter moiety in Zhou's method with any of substituted or non-substituted morpholine, piperidine or piperazine reported disclosed by Van Ness, because they all have the same functional groups, which are essential for creating labels in MS/MS analysis of peptides and nucleic acids.

Regarding claims 7-8 and 15 Zhou discloses analysis of peptides obtained by tryptic digest of yeast proteins (see page 514, right column, third paragraph).

Regarding claims 47 and 50-51 Zhou teaches that the reporter moieties were attached to solid support via photocleavable linkers (see Figure1), with solid supports being aminopropyl-coated glass beads, which were washed after the reaction of the reporter moieties having the linking groups with the beads (see Figure 1 and page 514, left column, first paragraph).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Y. Kim can be reached on (571) 272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

5/13/2009